DETAILED ACTION

1. Claims 23-33 are pending.

Response to Arguments and Remarks

2. Applicant's representatives arguments filed on July 23, 2009 have been fully considered but they are not persuasive, and the rejection of claims 23-33 under 103(a) is maintained. The "inhibiting…..VEGF-A…." limitation has been addressed previously. The discovery of the way that a prior art method operates when the method steps are obvious, does not impart patentability. The overall invention of treating angiogenesis is obvious as demonstrated by the examiner, and any mechanistic discoveries do not take away from the obviousness of the actual method steps which do not change regardless of new descriptions of interactions that were not previously known. Several of the arguments of counsel have been addressed before and the previous discussion will not be repeated here.

The discovery of the way that a prior art method operates when the method steps are obvious, does not impart patentability. The overall invention of treating angiogenesis is obvious as demonstrated by the examiner, and naturally flow from the properties of the compound disclosed in the art as shown by the secondary references. Mechanistic discoveries do not take away from the obviousness of the actual method steps, which do not change regardless of new descriptions of interactions that were not previously known. The double patenting rejections are also maintained for these reasons. The rejection for solvate is withdrawn.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over U. S. patent 6,498,169 (cited on the IDS) in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) Determining the scope and contents of the prior art: The '169 patent teaches the elected species of the instant case, moreover the '169 patent also teaches that the elected species and other compounds of the instant case are inhibitors of endothelial cell adhesion (column 118 - 119, Table 1). Bickwell teaches that "alignment of endothelial cells into tube-like structures" or adhesion of these cells to one another, is a key step in angiogenesis. Moreover Bicknell teaches that angiogenesis is important for the growth of solid tumors.

B) Ascertaining the differences between the prior art and the claims at issue.

The process of the instant case involves the "inhibiting angiogenesis" and treating solid tumors with 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl] methyl] piperidine, while the prior art teaches the inhibition of cell adhesion with 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl] methyl] piperidine. It goes without saying that the compounds and their method of administration is identical. It would appear then that the applicant seems to believe that a new property has been discovered.

C) Resolving the level of ordinary skill in the pertinent art: The level of ordinary skill is high. Someone using these compounds would be a medical doctor.

D) Considering objective evidence present in the application indicating obviousness or nonobviousness: One of ordinary skill would have realized based on the teachings of Bicknell et. al. that inhibitors of endothelial cell adhesion would also find use as angiogenesis inhibitors and for the treatment of solid tumors. It is well understood in the art that cell alignment and angiogenesis in general necessarily involve cell adhesion and the following reference is submitted to show that in fact when one is speaking of the alignment of endothelial cells and angiogenesis, adherence is necessarily taking place:

"Endothelial cell proliferation is a major component of angiogenesis, but is only one of a series of tasks the endothelial cells must accomplish to form a new capillary blood vessel. In response to angiogenic stimuli, endothelial cells degrade the extracellular matrix (ECM),[1] migrate into the perivascular space, proliferate, and align themselves into patent blood vessels. When sufficient angiogenesis has occurred, the endothelial cells become quiescent and the vessels either remain or regress if no longer needed. **During these events, the endothelial cells must adhere to one another** and to the ECM to construct and extend new microvessels." Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376. (pg. 373 paragraph 2)

Cell adhesion between leukocytes and endothelial cells alone can in fact be a requirement of angiogenesis as shown by the following citation:

"**However, angiogenesis sometimes depends on the interaction of endothelial cells with other types of cells**, and the roles of cell adhesion molecules in such interaction remain to be studied. It is noteworthy that the in vitro angiogenesis of bovine aortic endothelial cells induced by polymorphonuclear leukocytes requires adhesion of leukocytes to endothelial cells through E-selectin and integrin/intercellular adhesion molecule-1 interaction (44, 45). When added to the coculture of F-2 cells with A431 cells, the anti-sialyl Lex/Lea antibodies as well as anti-β1-integrin antibody significantly inhibited the interaction of endothelial cells with cancer cells. The orderly formation of cancer cell nests surrounded by functional vascular networks of F-2 cells was almost completely inhibited by these antibodies both in vitro and in vivo. **Our results indicated that the interaction of cancer cells with endothelial cells through adhesion molecules such as selectins and integrins is critical for generation of functional vascular networks nourishing cancer cell nests and promoting in vivo growth of tumors.** The novel in vitro and in vivo model experimental systems described here offer a unique opportunity to study direct or indirect interaction between cancer cells and endothelial cells together with the outcome." Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296.

The prior art '169 patent teaches that HUVECs stimulated with the cyctokine TNF-alpha become adherent to U937 cells and that the compounds of the instant invention block this adherence. The HUVECs are epithelial cells widely used in studies of angiogenesis. The U937 cells are lymphatic cancer cells. Clearly given the close connection between angiogenesis and cell adhesion, as shown above only one conclusion can be reached that invention as a whole is obvious over the prior art. A person of ordinary skill in the art would have been motivated to do so based on the desire to treat tumors which are not desirable tissues. The discovery of the way that a prior art method operates when the method steps are obvious, does not impart patentability. The overall invention of treating angiogenesis is suggested in the art, any mechanistic discoveries do not take away from the obviousness of the actual method steps which

do not change regardless of new descriptions of interactions. Inhibition of VEGF-A is an inherent, inevitable result of the practice, and while not discovered in the prior art, discovery of details how an obvious process operates does not change the conclusion of obviousness.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-17 of U.S. Patent No. 6,395,753 in view of in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '753 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

5. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-20 of U.S. Patent No. 6,498,169 in view of in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '169 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

6. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3 of U.S. Patent No. 6,605,620, in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims

although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '620 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

7. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-17 of U.S. Patent No. 6,867,221 in view of in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '221 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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